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Corresponding Author
JenishBabu,
Department of General Medicine Sree Mookambika Institute of Medical Sciences College Kanyakumari, Tamil Nadu, India

Author Designation
[1,3,4]Junior Resident
[2]Associate Professor

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Effects of Iron on Blood Glucose Levels in Type 2 Diabetes Mellitus: A Study in Tertiary Care Centre

[1]A. Jenish Babu, [2]Thilagar, [3]Prem Kumar and [4]Yokesh
[1-4]Department of General Medicine Sree Mookambika Institute of Medical Sciences College Kanyakumari, Tamil Nadu, India

Abstract
Iron is an important mineral whose metabolism is tightly regulated in our body. Iron is capable of initiating oxidative stress when in excess. Type 2 Diabetes mellitus is achronic disorder of glucose metabolism with multiple causes. Ferritin is a protein that storesiron in the body. Iron can affect the metabolism of glucose by influencing insulin's release and actions. We aimed at determining and comparing the serum levels of Iron, Total iron binding capacity(TIBC) and Ferritin in T2DM and healthy subjects and to correlate these with blood glucose levels. It was a case control study, which involved 50 T2DM patients and 50 controls. The study was undertaken in Subbaiah Institute of Medical Sciences. Serum blood glucose, Iron, TIBC were estimated in auto analyser and serum ferritin was es timated by chemil umin escence method. Statistical analysis: Mann Whitney Utestand Median, interquartil erange was applied. Spearman'srh ocorrelation was applied for correlations. $p<0.05$ was considered as statistically significant. Blood sugar levels and serum Ferritin levels were increased significantly in cases. Whereas serum iron and TIBC were not significantly elevated in cases. Only Ferritin showeda significant positive correlation with blood sugar levels. Increased levels of iron can lead to oxidative damage and lead to complications in diabetes mellitus patients. Hence frequent monitoring of serum iron and ferritin levels isadvisableinT2DM.

INTRODUCTION

Type 2 diabetes mellitus is a metabolic disease which is chronic in onset. Beta cells of islet of Langerhans of the pancreas secrete less in sulinin T2DM. complete absence orrelative decrease in the levels of insulin leading to chronic hyperglycemia is the main observation inT2DM[1,2]. It is worth mentioning that in sulin resistance, dyslipidemia and low grade chronic in flammation are the key features of T2DM[3]. International diabetes federation had estimated in 2015 that globally 1 in 11 adults between20-79 years had DM. According to experts prevalence of DM is going to increase from 415-642 million by 2040. Low to middle-income population is expected to have a significant risein prevalence of DM. Since there is insulin resistance, glucagon levels increase leading tohypergly cemia in DM[4].

Iron is a crucial element to all cells. Iron can donate and accept electrons. Iron is an active redoxco factor for many important biochemical reactions. This redox property of iron makes it toxic element as it generates free radicals, when it is in excess. That's why iron metabolism and absorption is tightly regulated by various mechanisms. Iron is an one way element. Excess iron can be toxic as it generates reactive oxygen species. The most important reaction which generates ROS is the Fent on reaction[5].

The human body has various detoxification processes to neutralize ROS. If the ROS are not neutralized effectively then they can cause damage to cellular components. Excess iron and ROS cause cell membrane damage and lead to pathological processes[6]. ROS induced by iron over load in terferes with in sulin signaling and causes impairment in translocation of Glucose tran sporter 4 to the cell membrane and impairs in sulin up take[5].

Insulin is shown to have its action on iron metabolism by exerting its action on glucose transport. Insulin helps in redistribution of transferring receptors from inside the cells to cellsurface and helping in uptake of iron by adipocytes. There are also studies showing that iron in terferes with insulin action by inhibiting insulin's action on hepatic glucose production. Increased iron also causes reduction in production of insulin and metabolism causing increased levels of insulin[7,8].

Iron is stored in the body mainly in the form of protein, ferritin. Ferritin is a spherical shaped protein, present inside the cell ,which can store up to 4000 iron atoms. Ferritin is secreted in to plasma in small quantity. This plasma concentration of ferritin usually depends on body iron stores, when there is no inflammation[9].

Objectives:

- To determine and compare the serum levels of Iron, Total iron binding capacity and ferritin in T2DM and healthy subjects.
- To correlate levels of blood glucose with Iron, Total iron binding capacity and ferritin.

MATERIALS AND METHODS

Study was designed as case control study. Study setting was in medicine out patient department of Subbaiah Institute of Medical Sciences, Shimoga. We included 100 subjects in the study. Among 100, 50 were cases of T2DM and 50 were age and sex matched healthy in dividuals as controls. Simple random sampling technique was chosen. Sample size was calculated by convenient sampling. Study duration was from October 2018 to march 2019. Institutional ethical clearance was taken before commencing the study.

Inclusion Criteria:

Cases: 50 subjects were cases. T2DM patients, diagnosed by physicians using American diabetes association criteria (10), age group of 30-65 years, who were taking oral anti hyperglycemic drugs were inclouded in study. They gave consent for the study.

Controls: age and sex matched 50 apparently healthy in dividuals.

Exclusion Criterias: Patients of diabetes having complications, Severe inflammatory diseases, infections, hepatic or renal diseases and persons on drugs that would affect blood glucose levels, Blood loss, blood transfusions and blood donation in last 6months duration, subjects on Iron supplements, chronic alcoholics, thyroid dysfunction, pregnant and lactating women. Methodology: Information was obtained by preformed questionnaire. Basic investigations were using standard protocol. Informed and written consent was taken from all subjects. A sample of 5ml venous blood was collected under aseptic conditions to study the following parameters

- Blood sugar by Glucoseoxidase-peroxidedase method. [11]-kits supplied by Robonik.
- Serum Iron and Total iron binding capacity by Ferrozine method. [12]-kits supplied by Coralcrest diagnostics.
- Serum Ferritin by chemiluminescence method. [13]-kits supplied by Minividas.

Blood sugar was measured in autoanalyzer Autora, serum Iron and TIBC were measured in semi auto analyser Robonik and serum Ferritin was measured in Hormone analyser Minividas.

Table/Fig1:ComparisonofFBS,PPBS, Serum Iron, TIBC and Serum Ferritin in cases and controls.

		Median	Percentile25	Percentile75	p-value
FBS mg/dl	Cases	137.8	121.7	178.15	<0.0005**
	Controls	85.5	74	96	
PPBS mg/dl	Cases	199.3	174.4	246.05	<0.0005**
	Controls	117	110.5	124	
Serum Iron microgm/dl	Cases	99.55	71.75	132.05	0.428
	Controls	98.1	78.9	104.35	
TIBC microgm/dl	Cases	278.4	255.15	321.25	0.07
	Controls	298.15	265.35	349.9	
Serum Ferritinng/ml	Cases	233.3	146.9	256.3	<0.0005**
	Controls	47.55	36.3	64.25	

<0.0005**Highly statistically significant.

Table/Fig 2 : Spearman's rho correlation between blood sugar levels and Iron, TIBC, Ferritin in cases.

	Iron	TIBC	Ferritin
FBS	0.201	-0.42	0.773**
PPBS	0.192	-0.51	0.710**

**correlation coefficient at 0.01level.

Statistical Analysis: Data was expressed as Mean±SD and was analysed in SPSS software version 20. Mann whitney Utest and Median, interquartile range was applied as values were in extreme range. Spearman's rho correlation was applied for correlations. p<0.05 was considered as statistically significant.

RESULTS AND DISCUSSIONS

Table/Fig 1 is showing comparison of FBS,PPBS, Serum Iron, TIBC and Serum Ferritin in cases and controls. Levels of FBS, PPBS and serum Ferritin were elevated in cases compared to controls and showed statistically high significance.

Table/Fig 2 is showing Spearman's rho correlations between FBS,PPBS and Serum Iron,TIBC, Serum Ferritin levels in cases. Ferritin showed highly statistically significance with FBS, PPBS levels.

We are seeing awareness among urban population about nutritional benefits of trace elements, now a days. Researchers and even clinicians are interested in knowing the association of trace elements with T2DM because the disease has multifactorial causes in onset, progression and development of complications[14]. Insulin resistance is a well known finding in T2DM and there are many evidences to show a link to elevated iron stores[15]. Ferritin is a storage protein for body iron stores and also a known inflammatory marker[16,17]. Ferritin stores iron in ferric state and protects cells from oxidative damage[2,18,19] At normal concentrations also iron influences glucose metabolism. Elevated levels of iron and thus ferritin cause insulin resistance by deposition in liver. Insulin is supposed to act in a duplex way. insulin helps in synthesis of ferritin and facilitates uptake of iron by intestinal cells and adipocytes[20] On the other hand iron influences insulin's actions on hepatic glucose output. Excess Iron is also found to affect skeletal muscles, which is the chief regulator of insulin actions[21]. Iron is a strong oxidant and can accelerate the synthesis of ROS. These ROS interfere with functions of beta cells of pancreas and affect insulin secretion and actions[2]. Excess iron can also affect mitochondria and thus production of ATP leading to glucose metabolism disorders[3,22-24].

Hepcidin is a peptide which is involved in iron regulation.it is secreted when insulin is secreted from beta cells. So it can be considered that iron concentration in blood is regulated by serum glucose levels, because when glucose level increases insulin is secreted and hepcidin is also released and it regulates iron release in to blood[2].

In this study we have tried to find out the association of hyperglycemia with iron profile parameters. In our study it was seen that serum iron In cases and controls showed no statistical significance. Same result was obtained in other studies[3,20,25].

In our study we found elevated ferritin levels in cases. Reasons for the elevation could be decreased clearance of glycosylated ferritin from blood in T2DM patients[26]. Similar finding was found in other studies[27-30].

In our study we found normal iron stores and increased ferritin levels in cases, which suggests probably ferritin acts as an antioxidant sequestering all free iron into the cells and protecting cells from oxidative damage[30].

We found significants pearman's rho correlation between blood sugars and serum ferritin levels in T2DM.

CONCLUSION

Serum ferritin was positively correlated to blood glucose levels indicating its association in development of disease. So it can be used as an indicator in predicting the risk of future complications. Measures can be taken to reduce the levels of iron if it is elevated in diabetes mellitus patients. Inadvertent use of iron prophylaxis without checking blood glucose levels should be discouraged in health centres.

Limitations: A further study with more sample size could show better correlation. Glycemic control and transferring saturation were no test imated. Prospective studies can be under taken to study role of ferritin in development of complications of DM.

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